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MESSAGE:

Applicant: Mark Hirsh

Serial No.: 10/012,202

Art Unit: 1615

Filed: December 5, 2001

Examiner: H. N. Sheikh

For: COMPOSITION CONTAINING BOTH SEDATIVE AND NON-SEDATIVE
ANTIHISTAMINES

1617926_v1

PTO/SB/21 (08-03)

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| TRANSMITTAL FORM (to be used for all correspondence after initial filing) | Application Number | 10/012,202 |
| | Filing Date | December 5, 2001 |
| | First Named Inventor | Mark Hirsh |
| | Art Unit | 1615 |
| | Examiner Name | H. N. Sheikh |
| Total Number of Pages in This Submission | Attorney Docket Number | CP 103 |

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☒ Applicant claims small entity status. See 37 CFR 1.27

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|----------------------|------------------|
| Application Number | 10/012,202 |
| Filing Date | December 5, 2001 |
| First Named Inventor | Mark Hirsh |
| Examiner Name | H. N. Sheikh |
| Art Unit | 1615 |
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| 1003 530 | 2003 265 | Plant filing fee | |
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| 1005 160 | 2005 80 | Provisional filing fee | |
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| Independent | -20* = | X | |
| Multiple Dependent | -3** = | X | |

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| 1202 18 | 2202 9 | Claims in excess of 20 |
| 1201 86 | 2201 43 | Independent claims in excess of 3 |
| 1203 290 | 2203 145 | Multiple dependent claim, if not paid |
| 1204 86 | 2204 43 | ** Reissue independent claims over original patent |
| 1205 18 | 2205 9 | ** Reissue claims in excess of 20 and over original patent |
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant: Mark Hirsh

Serial No.: 10/012,202

Art Unit: 1615

Filed: December 5, 2001

Examiner: H. N. Sheikh

For: *COMPOSITION CONTAINING BOTH SEDATIVE AND NON-SEDATIVE
ANTIHISTAMINES*

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APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 1-29 in the Office Action mailed July 21, 2003, in the above-identified patent application. A Notice of Appeal was mailed on December 19, 2003, along with a Response to the Office Action. The Commissioner is hereby authorized to charge \$165.00 for the filing of this Appeal Brief, which is the appropriate fees for a small entity, to Deposit Order Account No. 50-1868. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-1868.

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(1) REAL PARTY IN INTEREST

The real party in interest of this application is the assignee Peirce Management, LLC, Wellesley, MA.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS ON APPEAL

Claims 1-29 are pending and on appeal.

(4) STATUS OF AMENDMENTS

The claims were last amended in the amendment mailed on May 15, 2003. Appendix I sets forth the claims on appeal.

(5) SUMMARY OF THE INVENTION

A combination formulation of (1) a non-sedating antihistamine which inhibits histamine release for a period of either 4 to 12 hours or 10 to 20 hours and (2) a sedating antihistamine which inhibits histamine release for a period of either 10 to 20 or 4 to 12 hours, which is not released from the formulation for 6 to 10 or 8 to 12 hours after administration. See pages 7 to 8.

(6) ISSUES ON APPEAL

The issues presented on appeal are:

(a) whether claims 1-29 are obvious under 35 U.S.C. 103 over U.S. Patent No. 5,451,409 to Rencher et al. ("Rencher"); and

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(b) whether claims 1-29 are obvious under 35 U.S.C. 103 over U.S. Patent No. 5,827,852 to Russell, et al., or U.S. Patent No. 5,648,358 to Mitra, et al. in combination with Rencher.

(8) ARGUMENTS

(a) The Claimed Invention

The claims define a biphasic antihistamine composition in daily oral uni-dosage or divided dosage form and a method of making and using the composition. The dosage form contains **two monophasic parts**, each having an active ingredient which is either a sedating antihistamine or a non-sedating antihistamine (p. 7, line 15 to p. 8, line 9). The claimed composition has the advantage of (1) avoiding sedating effects of sedating antihistamine during the day time and (2) taking the full advantage of sedating antihistamine in the night time (p. 9, lines 5-13), while only needing to be administered once a day. The claimed composition achieves this advantage by being formulated so that only non-sedating antihistamine is released in the day, and only sedating antihistamine is released at night (p. 8, line 10 to p. 9, line 4). Various delayed or sustained release formulations and coatings (p. 10, lines 9-25; p. 13, lines 1-13; p. 13, line 18 to p. 28, Examples 1-3) are used to achieve this release profile.

Dependent claims are drawn to compositions comprising specific sedating antihistamines (claims 2, 3, 14 and 15) or a therapeutically effective amount of an additional agent (claims 8, 19, 25, 28 and 29). The composition can have a specific release profile of the sedating or non-sedating antihistamine or the additional agent (claims 4-7 and 16-18). The sedating or non-sedating antihistamine can be formulated into a sustained release form or a delayed release form (claims 24-27 and 29) using at

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least one delayed release control polymer or at least one sustained release control polymer defined therein.

As shown in Examples 1-3, procedures are taken to ensure the biphasic feature of the composition such that the sedating antihistamine is released in the night or evening time but not released in the day time and the non-sedating antihistamine is released in the day time but not released in the night time.

(b) Rejections Under 35 U.S.C. § 103

The Legal Standard

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that: (i) the prior art suggests the claimed invention; and (ii) the prior art indicates that the invention would have a reasonable likelihood of success. *In re Dow Chemical Company*, 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988).

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). The

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Court of Appeals for the Federal Circuit warned that “the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for showing of the teaching or motivation to combine prior art references.” *In re Dembiczak*, 175 F.3d 994 at 999 (Fed. Cir. 1999). The “question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. *WMS Gaming, Inc. v International Game Technology*, 184 F.3d 1339 at 1355 (Fed. Cir. 1999). “[T]he showing must be clear and particular.” *In re Dembiczak*, 175 F.3d 994 at 999 (Fed. Cir. 1999). Although with the answer in hand, the “solution” now appears obvious, that is not the test. The references must themselves lead those in the art to what is claimed. And in this case, there is simply no such teaching.

The Prior Art

Rencher

Rencher describes a single “homogeneous matrix” containing one or more actives, from which each active component is released at an appropriate rate to provide the desired activity over a period of 2 to 24, preferably 8 to 12 hours (col. 2, lines 21-27). The formulation uses a polymer blend of hydroxypropyl cellulose (HPC) and hydroxyethyl cellulose (HEC) to control the release rate of the active components (col. 1, line 60 to col. 2, line 5). It is important to note that the composition, upon administration, provides sustained; *not delayed*, release, releasing the active component at a rate to provide the desired activity over a period of 2 to 24 hours (col. 2, lines 26-27). The active component is released immediately at an effective level and remains such over a period of 2 to 24 hours. This is clearly seen in Tables 6 and 8, which shows that the

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composition can release 15 to 26 percent of the active component within 30 minutes after administration.

Russell

Russell describes a pharmaceutical composition suitable for coating a drug for treating cold, cough, allergy, and flu symptoms (col. 2, lines 42-67). The active ingredient can be an antihistamine (col. 5, lines 37-42). The composition can be formed of triturate active ingredients which are "blended together" (col. 7, line 45 to col. 8, line 67, particularly col. 8, lines 33-35, Examples I-III). The active ingredients in a composition of a blend of triturate active ingredients do not distinguish one from another in terms of the timing and the rate of release. Therefore, the composition described in Russell, without more, would not delay the release of any of the active ingredients. It certainly cannot prevent the release of one of the active ingredient in the day time.

Mitra

Mitra describes antihistamine preparations which must contain caffeine, a stimulant (col. 2, line 24). This is the antithesis of what applicants claim: a biphasic composition that allows one to obtain the benefit of an antihistamine while sleeping, and the benefit of a non-sedating antihistamine while active. Indeed the goal of Mitra's formulation is to prevent the sleepiness due to the use of an antihistamine! (see col. 2, lines 61-67)

The Art Alone or in Combination

Rencher fails to make obvious the claimed subject matter because Rencher does not recognize the benefit of a formulation containing both a sedating antihistamine and a non-sedating antihistamine, which are released at different time periods. Moreover,

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Rencher teaches making a homogeneous composition of the active ingredients. In contrast, as the foregoing discussion shows, a biphasic composition as defined in any of the claims 1-29 is necessary to achieve the release profile defined in claims of the present application. Therefore, even if one could find a reference providing the motivation to combine a sedating with a non-sedating antihistamine, Rencher would not lead one of ordinary skill in the art to have a reasonable expectation of success of the claimed composition and method of using the composition. Further, in emphasizing a homogeneous composition, Rencher teaches away from the claimed biphasic composition.

Russell teaches forming a simple blend of triturate active ingredients while Rencher teaches forming a homogenous composition. Therefore, Russell in combination with Rencher, fails to teach one skilled in the art to make a biphasic composition, for delivery of a sedating antihistamine during the night and a non-sedating antihistamine during the day time.

Accordingly, Russell in view of Rencher would not render claims 1-29 *prima facie* obvious under 35 U.S.C. 103.

Mitra's formulation *never allows one to sleep - the caffeine is a stimulant*. If one combined Mitra's formulation into a biphasic composition, one would not achieve appellant's goal. Therefore the claimed subject matter, alone or in combination with Rencher cannot be obvious from Mitra.

The examiner's rejections have been conclusory and apparently made only by reference to claim 1. None of the prior art defines time periods in which antihistamine activity – either sedating or non-sedating activity is desirable, as required by the

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independent claims, as well as claims 4, 5, 16, 17, and 22. None of the art teaches combining a sedating and a non-sedating antihistamine, much less the selection of the specific medications defined by claims 2, 3, 14, and 15. None of the art recognizes that one may add other medications, such as an analgesic that is released in only one or both of the two phases of the formulation, as defined by claims 25, 26, 28 and 29, for example, so that it is released immediately or in a delayed or sustained release fashion. Indeed, the examiner appears to have ignored the additional limitations of the dependent claims.

(9) SUMMARY AND CONCLUSION

In summary, none of the art motivates one skilled in the art to make a biphasic composition containing a sedating antihistamine in a first portion and a non-sedating antihistamine in a second portion where release is delayed.

The examiner has used hindsight to provide motivation. This is improper, however. It is well established that the motivation *must* come from the references themselves. In this case, at least one of the references actually teaches away from what applicants have developed, and none recognize the potential benefit or desirability of a two phase formulation. Therefore the subject matter of claims 1-29 is not obvious.

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For the foregoing reasons, Appellant submits that the claims 1-29 are patentable.

Respectfully submitted,



Patrea L. Pabst
Reg. No. 31,284

Date: December 18, 2003

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Appendix: Claims On Appeal

1. (original) A biphasic antihistamine composition in daily oral uni-dosage or divided dosage form which comprises:

(a) a therapeutically effective amount of a sedating antihistamine to inhibit histamine release for a duration of about 4 to 12 hours, and

(b) a therapeutically effective amount of non-sedating antihistamine to inhibit histamine release for a duration of 10 to 20 hours, with a delayed release 6 to 10 hours after ingestion.

2. (original) The antihistamine composition defined in claim 1 wherein the sedating antihistamine is selected from the group consisting of brompheniramine, chlorpheniramine, debrompheniramine, dexchlorpheniramine, carbinoxamine, clemastine, diphenhydramine, pyrilamine, tripeleminamine, triprolidine, methdilazine, bromodiphenhydramine, promethazine, azatadine, cyproheptadine, diphenylpyraline, doxylamine, trimeprazine, phenindamine, ketotifen, hydroxyzine, tazifylline, temelastine, meclizine, acrivastine, setastine, oxatomide, mequitazine, levocabastine, lodoxamide, AHR 11325, phenindamine, azelastine, and ebastine, or a pharmaceutically acceptable salt thereof.

3. (original) The antihistamine composition defined in claim 1 wherein the non-sedating antihistamine is selected from the group consisting of fexofenadine, loratadine, descarboethoxy loratadine, astemizole, norastemizole, desmethylastemizole, cetirizine, acrivastine, and temelastine, or a pharmaceutically acceptable salt thereof.

4. (original) The antihistamine composition defined in claim 1 wherein the sedating antihistamine has a duration of activity of about 6 to 10 hours.

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5. (original) The antihistamine composition defined in claim 1 wherein the non-sedating antihistamine has a duration of activity of about 12 to 18 hours.

6. (original) The antihistamine composition defined in claim 1 wherein the sedating antihistamine is releasable immediately or up to 1 hour following administration.

7. (original) The antihistamine composition defined in claim 1 wherein the non-sedating antihistamine is releasable immediately or up to 1 hour following administration.

8. (original) The antihistamine composition defined in claim 1 which further comprises a therapeutically effective amount of at least one agent selected from the group consisting of an analgesic agent, an antitussive agent, an expectorant, an anti-inflammatory agent, an anti-pyretic agent and a decongestant.

9. (original) A method of inhibiting the release of histamine in a patient which comprises the step of administering to the patient, a therapeutically effective amount of the antihistamine composition defined in claim 1.

10. (original) The method of inhibiting the release of histamine defined in claim 9 wherein the antihistamine composition is administered during the evening or night and the sedating antihistamine is immediately released.

11. (original) The method of inhibiting the release of histamine defined in claim 9 wherein the antihistamine composition is administered during the evening or night and the non-sedating antihistamine is released the next day, 6 to 10 hours following administration.

12. (original) The method of inhibiting the release of histamine defined in claim 9 wherein the patient suffers from allergic reaction, allergic rhinitis, cold or flu.

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13. (original) A biphasic antihistamine composition in daily oral uni-dosage or divided dosage form which comprises:

(a) a therapeutically effective amount of a non-sedating antihistamine to inhibit histamine release for a duration of about 10 to 20 hours, and

(b) a therapeutically effective amount of sedating antihistamine to inhibit histamine release for a duration of 4 to 12 hours, with a delayed release, 8 to 12 hours after ingestion.

14. (original) The antihistamine composition defined in claim 13 wherein the non-sedating antihistamine is selected from the group consisting of fexofenadine, loratadine, descarboethoxy loratadine, astemizole, norastemizole, desmethylastemizole, cetirizine, acrivastine, and temelastine, or a pharmaceutically acceptable salt thereof.

15. (original) The antihistamine composition defined in claim 13 wherein the sedating antihistamine is selected from the group consisting of brompheniramine, chlorpheniramine, debrompheniramine, dexchlorpheniramine, carbinoxamine, clemastine, diphenhydramine, pyrilamine, tripeleannamine, tripolidine, methdilazine, bromodiphenhydramine, promethazine, azatadine, cyproheptadine, diphenylpyraline, doxylamine, trimeprazine, phenindamine, ketotifen, hydroxyzine, tazifylline, temelastine, meclizine, acrivastine, setastine, oxatomide, mequitazine, levocabastine, lodoxamide, AHR 11325, phenindamine, azelastine, and ebastine, or a pharmaceutically acceptable salt thereof.

16. (original) The antihistamine composition defined in claim 13 wherein the non-sedating antihistamine has a duration of activity of about 12 to 18 hours.

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17. (original) The antihistamine composition defined in claim 13 wherein the sedating antihistamine has a duration of activity of about 6 to 10 hours.

18. (original) The antihistamine composition defined in claim 13 wherein the non-sedating antihistamine is releasable immediately or up to 1 hour following administration.

19. (original) The antihistamine composition defined in claim 13 which further comprises at least one agent selected from the group consisting of an analgesic agent, an antitussive agent, an expectorant, an anti-inflammatory agent, an anti-pyretic agent and a decongestant.

20. (original) A method of inhibiting the release of histamine in a patient which comprises the step of administering to the patient, a therapeutically effective amount of the antihistamine composition defined in claim 13.

21. (original) The method of inhibiting the release of histamine defined in claim 20 wherein the antihistamine composition is administered during the day and the non-sedating antihistamine is immediately released.

22. (original) The method of inhibiting the release of histamine defined in claim 20 wherein the antihistamine composition is administered during the day and the sedating antihistamine is released in the evening or night, 8 to 12 hours following administration.

23. (original) The method of inhibiting the release of histamine defined in claim 20 wherein the patient suffers from allergic reaction, allergic rhinitis, cold or flu.

24. (original) The antihistamine composition defined in claim 1 wherein the delayed release portion is achieved by coating a core or granulations with at least one delayed release control polymer selected from the group consisting of ethyl cellulose,

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cellulose acetate, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, acrylic acid polymers and copolymers, polymers or copolymers of methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate, ethyl methacrylate, hydroxypropyl methylcellulose acetate succinate, shellac, cellulose acetate trimellitate, vinyl acetate, azo polymers, pectin, chitosan, amylose, guar gum, and zein or combination thereof.

25. (original) The antihistamine composition defined in claim 8 wherein the analgesic agent, antitussive agent, expectorant, anti-inflammatory agent or decongestant is in a sustained release form.

26. (original) The antihistamine composition defined in claim 25 wherein the sustained release effect is achieved by formulating the analgesic agent, antitussive agent, expectorant, anti-inflammatory agent or decongestant with a sustained-release control polymer selected from the group consisting of methyl cellulose, ethyl cellulose, wax, gums, cellulose acetate, cellulose acetate phthalate, hydroxypropylmethylcellulose succinate, polyvinyl acetate phthalate, acrylic acid polymers and copolymers, polymers or copolymers of methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate, ethyl methacrylate, hydroxypropyl methylcellulose acetate succinate, shellac, cellulose acetate trimellitate, vinyl acetate and combination thereof.

27. (original) The antihistamine composition defined in claim 13 wherein the delayed release portion is achieved by coating a core or granulations with at least one delayed release control polymer selected from the group consisting of ethyl cellulose, cellulose acetate, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, acrylic acid polymers and copolymers, polymers or

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copolymers of methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate, ethyl methacrylate, hydroxypropyl methylcellulose acetate succinate, shellac, cellulose acetate trimellitate, vinyl acetate, azo polymers, pectin, chitosan, amylose, guar gum, and zein or combination thereof.

28. (previously presented) The antihistamine composition defined in claim 19 wherein the analgesic agent, antitussive agent, expectorant, anti-inflammatory agent or decongestant is in an immediate release form or in a sustained release form.

29. (original) The antihistamine composition defined in claim 28 wherein the sustained release effect is achieved by formulating the analgesic agent, antitussive agent, expectorant, anti-inflammatory agent or decongestant with a sustained-release control polymer selected from the group consisting of methyl cellulose, ethyl cellulose, wax, gums, cellulose acetate, cellulose acetate phthalate, hydroxypropylmethylcellulose succinate, polyvinyl acetate phthalate, acrylic acid polymers and copolymers, polymers or copolymers of methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate, ethyl methacrylate, hydroxypropyl methylcellulose acetate succinate, shellac, cellulose acetate trimellitate, vinyl acetate and combination thereof.

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Certificate of Mailing

Appendix I: Claims On Appeal

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